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November 22, 2000

Via Certified Mail, Return Receipt Requested

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Nos. 00P-1275 and 00P-1276

Written Comments to Interim Final Rule "Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease" (65 Fed. Reg. 54686 (September 8, 2000))

Dear Sir or Madam:

On behalf of Traco Labs, Inc.("Traco"), we are submitting in duplicate the following written comments on FDA's Interim Final Rule, "Food Labeling: Health Claims; Plant Sterol/Stanol Esters and Coronary Heart Disease" published in the Federal Register of September 8, 2000 (65 Fed. Reg. 54686).

Traco supports FDA's position in authorizing use of a health claim on the association between plant sterol/stanol esters and reduced risk of coronary heart disease ("CHD"). However, it believes authorized use of the health claim should be expanded.

Areas for Expansion

First, Traco believes authorization should be expanded to allow use of the health claim for plant sterols (free sterol form) on the labels and labeling of food and dietary supplements.

Second, Traco believes authorization should be expanded to allow use of the health claim for plant sterols (free sterol form) in a wide variety of dosage forms for dietary supplements, to

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include tablets, capsules, softgel capsules, and chewable wafers. This would allow for a better dosing pattern since it can be taken with every meal.

Third, Traco believes the authorized use of this health claim should be expanded to apply to a variety of conventional foods. As long as the food complies with other health claim requirements, Traco believes the food choice should be unrestricted; that is, it should be expanded to include a variety of conventional food delivery systems.

We believe this expansion is reasonable and warranted, based on the totality of publicly available evidence referenced in the interim final rule itself and listed in Attachment 1 to this letter. You will notice that several of the references in our Attachment 1 coincide with the references in the interim final rule itself. We have also included in Attachment 2, the results of an unpublished study entitled "Cholestatin® Phytosterols: 400 mg. Chewable Tablet Dosage Form Clinical Trial," sponsored by Traco Labs, Inc.

Introduction

The use of the health claim for plant sterols should be immediately allowed. In the interim final rule, FDA recognized that plant sterols are the active moiety of plant sterol esters. The required dosage of 1.3g plant sterol esters daily is based on the equivalent dosage 0.8g plant sterols per day. 65 Fed. Reg. at 54690 and 54704.

The use of dietary supplement dosage forms should be immediately allowed as well. In the interim final rule FDA recognizes that dietary supplement dosage forms are safe and effective based on the allowance of the health claim for plant stanol esters in softgel capsules. 65 Fed. Reg. at 54708.

The delivery forms allowed in the interim final rule accommodate plant sterol esters that are fat soluble (comprised of approximately 37.5% fat and 63.5% plant sterols) and require delivery in a fat-based system (spreads and salad dressings). As a result, FDA made exception to the low fat requirement for heart disease health claims. Plant sterols reduce serum cholesterol values through competitive inhibition of cholesterol uptake at the time of ingestion; therefore, they are effective when delivered at the time of meals. In an effort to limit fat consumption, plant sterol ester intake is limited to twice per day under the current regulation. Because of their mechanism of action, plant sterols should be consumed with every meal in order to be most effective. Delivery of plant sterols, which need not be carried in fat, could be done with every meal as the scientific evidence suggests, without leading to over-consumption of dietary fat.

Traco's Position in Support of an Expanded Authorization of Use of the Health Claim

1. Authorizing Use of the Health Claim for Plant Sterols (Free Sterol Form)

a. The Preliminary Requirement of § 101.14(b)(3)(i) is Satisfied

The interim final rule provides:

> Under § 101.14(b)(3)(i), the substance that is the subject of a health claim must contribute taste, aroma, or nutritive value, or any other technical effect listed in § 170.3(o) (21 CFR 170.3(o)), to the food and must retain that attribute when consumed at the levels that are necessary to justify a claim. ...
>
> ...nutritive value "includes assisting in the efficient functioning of classical nutritional processes and of other metabolic processes necessary for the normal maintenance of human existence."

65 Fed. Reg. 54688.

It further states that based on the scientific evidence a "cholesterol-lowering effect of plant sterol esters is achieved through an effect on the digestive process [which] is one of the metabolic processes necessary for the normal maintenance of human existence. Therefore, the agency concludes that the preliminary requirement of §101.14(b)(3)(i) is satisfied." 65 Fed. Reg. at 54688.

Traco believes that the preliminary requirement of §101.14(b)(3)(i) is satisfied also for plant sterols. In the interim final rule, FDA "agrees that the active moiety of the plant sterol ester is the plant sterol and [concludes] that studies of the effectiveness of free plant sterols in blood cholesterol reduction are relevant to the evaluation of the evidence in the plant sterol esters petition." 65 Fed. Reg. at 54690.

Plant sterol esters are hydrolyzed to free sterols and fatty acids in the gastrointestinal tract, and free plant sterols are the active moiety of plant sterol esters. 65 Fed. Reg. at 54690. Accordingly, Traco believes that the literature on both free plant sterols and plant sterol esters is relevant.

Plant sterols (esterified or free) were tested in either a spread, margarine, or butter carrier and produced fairly consistent results regardless of the carrier and apparent differences in processing techniques. Given the variability of amounts and carriers in which plant sterols and plant sterol esters were provided, the response of blood cholesterol levels to plant sterols appears to be consistent and substantial. See discussion in Section III beginning at 65 Fed. Reg. at 54690.

Referenced in the interim final report are recent reports which indicate that beta-sitosterol and related compounds of plant sterols may be more effective in small doses with regard to blood cholesterol reduction than previously thought, and the fact that beta-sitosterol is approved for use as a drug to lower cholesterol. 65 Fed. Reg. at 54690.

Plant sterols in their free sterol form are primarily of the 4-desmethyl sterol class. These are the same plant sterols that have demonstrated a blood cholesterol-lowering effect. The major 4-desmethyl sterols are beta-sitosterol, campesterol and stigmasterol. Plant Sterols are extracted from plant sources, occur widely throughout the plant kingdom and are present in many edible fruits, vegetables, nuts, seeds, cereals, and legumes. 65 Fed. Reg. at 54687-88, and 54705.

These are the major sterols present in plant sterol esters, forming the active moiety of this substance. These plant sterols, when evaluated for compliance purposes, can be identified through gas-liquid chromatography by methodology validated by the American Oil Chemists Society (AOCS Official Method Ce 3-74). 65 Fed. Reg. at 54705.

Traco believes that the same basis for the agency's conclusion that the preliminary requirement of §101.14(b)(3)(i) is satisfied for plant sterol esters could be applied by the agency for the same conclusion with respect to plant sterols.

b. The Requirement of § 101.14(b)(3)(ii) is Satisfied

Traco believes that the requirement of § 101.14(b)(3)(ii) has been satisfied because the substance - plant sterols (free steorol form) - is safe and lawful. FDA evaluated Lipton's plant sterol esters and had no questions regarding Lipton's conclusion that vegetable oil sterol esters are GRAS under the intended use:

> A review of Lipton's ... submission and of its ... letter to the agency, ..., reveals significant evidence supporting the safety of the use of plant sterol esters at the levels necessary to justify a health claim. Moreoever, FDA is not aware of any evidence that provides a basis to reject the petitioner's position that the use of plant sterol esters in spreads and dressings for salad up to 1.6 g/serving is safe and lawful. ... [T]he level of plant sterol esters necessary to justify a claim is 1.3 g per day. Therefore, FDA concludes that the petitioner has satisfied the requirement of § 101.14(b)(3)(ii) to demonstrate that the use of plant sterol esters in spreads and dressings for salad at the levels necessary to justify a claim is safe and lawful.

65 Fed. Reg. at 54689.

Traco's same source plant sterols make up the active portion of plant sterol esters, and based on this, must be considered GRAS as well for the intended use. The level of plant sterol esters necessary to justify a claim is 1.3 g per day. The required dosage of 1.3g per of plant sterol esters daily is based on the equivalent dosage of 0.8g plant sterols per day. 65 Fed. Reg. at 54704. Traco believes that FDA should conclude that the requirement of § 101.14(b)(3)(ii) has been satisfied with respect to plant sterols, and that use of plant sterols at the levels necessary to justify a claim is safe and lawful.

Traco also believes that there is an adequate basis for FDA to conclude that a dietary supplement containing plant sterols (free sterol form) would be reasonably expected to be safe. It appears that the FDA concluded that the use of plant stanol esters in dietary supplements at the levels necessary to justify a claim is safe and lawful was based, in part, on the results of studies conducted in human to test hypocholesterolemic effects of plant stanol esters.

Consistent with FDA's discussion in Part IV of its interim final rule, based on the totality of publicly available scientific evidence, Traco believes there is significant scientific agreement to support a relationship between consumption of plant sterols and the risk of CHD. As stated in the interim final rule, "[t]he evidence that plant sterol esters affect the risk of CHD is provided by studies that measured the effect of plant sterol ester consumption on the two major risk factors for CHD, serum total and LDL cholesterol." 65 Fed. Reg. at 54700.

Traco believes it is reasonable to state that most intervention trials in subjects with mildly to moderately elevated cholesterol levels demonstrate the ability of free plant sterols, the active moiety of plant sterol esters, to reduce blood total and/or LDL cholesterol levels to a significant degree. HDL cholesterol levels remain unchanged. Moreover, results in normocholesterolemic subjects were similar. 65 Fed. Reg. at 54700-01.

For these reasons, Traco believes that there is an adequate basis for FDA to conclude that the requirement of § 101.14(b)(3)(ii) is satisfied with respect to the use of plant sterols (free sterol form) in dietary supplements at the levels necessary to justify a claim is safe and lawful.

c. The Exception is Not Applicable

Traco believes that the exception to the disqualifying level of total fat per 50g for heart disease health claim is not necessary for plant sterols as they are not embedded in a fat-based carrier. There is an additional health benefit to the consumer because the product is not fat-based.

2. Allowing a Wide Variety of Dosage Forms

Traco agrees with the agency that daily dosage of 0.8g plant sterols per day has consistently been shown to lower blood total and LDL cholesterol. This daily dosage is associated with reduced risk of CHD accordingly.

Traco believes that use of the claim as it relates to plant sterols should be expanded to include a variety of dietary supplements including, but not limited to tablets, capsules, softgel capsules, and chewable wafers for reasons of safety, efficacy, and ease of dose.

3. Expansion of the Eligible Types of Foods

Traco believes that the agency should authorize use of the health claim for plant sterols in all conventional foods, without restriction as to type of food, so long as analytical methodology exists that is suitable for quantification of plant sterols in that food.

As stated in the interim final rule, the agency has generally made the assumption that a daily food consumption pattern includes three meals and a snack. In previous CHD health claims (soy protein, soluble fiber), the agency concluded that the assumption of four servings per day of such foods was reasonable. Because of the lack of variety of sterol ester-containing foods, as well as the fact that these foods are necessarily fat-based, the agency does not believe four servings per day of plant sterol esters to be an appropriate dietary recommendation. By contrast, plant sterols, which can be delivered in systems that meet guidelines for low fat and low cholesterol (both dietary supplements and conventional foods), can be consumed with all meals. This allows for a more desirable dosage pattern without risk to public health. For this reason, we suggest that the recommended daily dosage of plant sterols be consumed in two to four servings, provided that the delivery system meets requirements for low fat and low cholesterol. Traco's suggestion would be consistent with FDA's position, as stated in the interim final rule at 65 Fed. Reg. at 54707.

Plant sterols can be delivered in systems meeting CHD health claim requirements for low fat, low saturated fat and low cholesterol. Traco believes these to be appropriate guidelines for conventional food delivery systems, and that use of the claim should be allowed for conventional foods meeting these requirements while delivering the suggested daily dosage.

As discussed in the FDA's interim final rule, dietary supplements are not subject to the minimum nutrient contribution requirement. FDA has determined that conventional foods are subject to the minimum nutrient contribution requirement, despite the fact that the effectiveness of plant sterols is not dependent upon the vitamin A, vitamin C, iron, calcium, protein or fiber content of the food. The minimum nutrient contribution requirement, coupled with CHD health claim requirements for low fat, low saturated fat and low cholesterol, will ensure that the use of conventional food delivery systems does not undermine the value of the claim by its use on foods of little or no nutritional value. See 65 Fed. Reg. at 54711.

Proposed Model Health Claim

Traco proposes that 21 CFR 101.83(e) be amended to add the following model health claim for foods or dietary supplements containing plant sterols:

> "800mg of plant sterols taken in two to four servings per day with meals may reduce the risk of heart disease. A serving of [name of product] supplies XXX mg of plant sterols."

Finally, to be consistent with the FDA's current authorization of the plant sterol/stanol esters and CHD health claim (made effective upon publication of the interim final rule on September 8, 2000), Traco requests that any expanded version of the proposed rule be effective immediately in order to further the stated purpose of helping consumers develop and maintain healthy dietary practices.

If you have any questions or require additional information regarding this submission, please do not hesitate to contact us.

Sincerely Yours,

ULLMAN, SHAPIRO & ULLMAN, LLP

Elizabeth Gioiosa Dillabough

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This reference is listed as Reference 25 in the FDA's interim final rule at 65 Fed. Reg. at 54715.

Cholestatin® Phytosterols:
400mg Chewable Tablet
Dosage Form Clinical Trial

Administrator	Charles Keenan, MD
Coordinator	Robert Kowalski
Sponsor	Traco Labs, Inc.
Location	Santa Monica-UCLA Medical Center Clinical Laboratories

Design	Open-label
Subjects	Twelve male and female patients age 35 - 70, with total cholesterol level falling in the moderate or high risk category (200 - 299 mg/dL) as defined by the American Heart Association.

Background

Phytosterols are a class of naturally occurring plant-derived compounds that are chemically analogous to cholesterol. They have been proven as an effective means to lower serum cholesterol levels, having an effect on LDL-cholesterol in particular. It is because of their structural similarity to cholesterol that phytosterols work by competitively inhibiting uptake of dietary and endogenous cholesterol. Phytosterols compete for sterol esterase enzymes and sterol receptor sites in the intestines, but unlike cholesterol, they are very poorly absorbed. As a result, they don't contribute to increased serum cholesterol levels. For this reason, phytosterols are most effective when consumed shortly prior to meals.

Study Objective

The effectiveness of phytosterols as a cholesterol lowering therapy is well understood and documented in medical literature. The purpose of this trial was not to prove that phytosterols lower cholesterol, but merely to confirm that the typical effects of phytosterols can be seen from a chewable tablet dosage form.

Methods

Fifteen subjects were initially screened, and baseline cholesterol profiles were determined. Twelve subjects met eligibility requirements and were enrolled in the trial.

Twelve subjects were given a 30-day supply (90 count) of Cholestatin® chewable tablets. They were instructed to take one tablet three times per day, prior to each meal. No other dietary restrictions or changes were required. A written copy of the instructions was also given to each subject. Subjects were instructed to return to the clinic within one week of completion of the tablets for a cholesterol screen.

Results

Seven subjects demonstrated appropriate compliance with the study instructions yielding viable data. The other five failed to complete the regimen or failed to return within the allotted time for follow-up screening so that any effect of phytosterols would have already been washed out.

On average, a 5% decrease in total cholesterol was observed. Perhaps more notable was the 10% decrease in LDL seen. As expected, HDL levels remained relatively flat

with a 3% overall increase. Even without a significant increase in HDL, a 6% improvement in the total cholesterol to HDL ratio was observed. The results are summarized in the following table.

	Total Cholesterol				HDL		LDL		TC:HDL
Patient	start	finish	start	finish	start	finish	start	finish	
1	221	227	41.0	41.2	156	153	5.3	5.5	
2	232	236	53.7	50.8	164	166	4.3	4.6	
3	256	236	54.1	64.4	161	142	4.7	3.6	
4	230	220	46.7	43.0	152	148	4.9	5.1	
5	260	217	50.1	52.4	174	126	5.1	4.1	
6	212	215	47.2	52.6	139	123	4.4	4.0	
7	280	259	53.4	51.4	181	153	5.2	5.0	
avg.	**241.6**	**230.0**	**49.5**	**50.8**	**161.0**	**144.4**	**4.8**	**4.6**	
% change			***-5%***		***+3%***		***-10%***		***-6%***

Conclusion

This trial was not designed to deliver conclusive evidence of the effectiveness of phytosterols, a fact that has previously been demonstrated. Rather, this trial was designed to show that the effectiveness of phytosterols translates to a chewable tablet delivery form. For this reason, as well as for time and economic purposes, an open-label design was used. As a result, compliance was not as keen as a highly controlled study.

From those subjects who did complete the trial, however, we were able to determine that 400mg phytosterol chewable tablets do in fact lead to a reduction in total cholesterol and LDL-cholesterol levels when taken prior to meals. In addition, HDL-cholesterol levels were not only maintained, but also slightly improved. True to form with previous published clinical data, phytosterols delivered in a chewable tablet not only lower total cholesterol, but also lead to the improvement of cholesterol profiles as demonstrated by changes in the TC:HDL ratio.

Encl. S1-S7 pre-screen & post-screen (14pp)